PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	
Karl Theodor KRAEMER et al.	Group Art Unit: 1617
Application No.: 09/425,742	
Filed: October 22, 1999	Examiner: Gina C. Yu
For: COMPOSITIONS FOR TOPICAL APPLICATION HAVING ANDROGENIC ACTIONS	Confirmation No.: 9957

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Submission of Translation of Priority Documents

Further to Applicants' claim for priority, the enclosed copies of English language translations of German priority applications Serial Nos. 198 48 856.4 and 199 00 749.7, filed October 23, 1998 and January 12, 1999, respectively, are provided herewith.

Please charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
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By: _____
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Reg. No. 48,638

Dated: November 20, 2008

UNITED STATES PATENT AND TRADEMARK OFFICE

I, Charles Edward SITCH BA,

Managing Director of RWS Group Ltd UK Translation Division, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare;

1. That I am a citizen of the United Kingdom of Great Britain and Northern Ireland.

2. That the translator responsible for the attached translation is well acquainted with the German and English languages.

3. That the attached is, to the best of RWS Group Ltd knowledge and belief, a true translation into the English language of the accompanying copy of the specification filed with the application for a patent in Germany on 23 October 1998 under the number 198 48 856.4 and the official certificate attached thereto.

4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application in the United States of America or any patent issuing thereon.

For and on behalf of RWS Group Ltd

The 19th day of February 2008

FEDERAL REPUBLIC OF GERMANY

Certificate

Hoechst Marion Roussel Deutschland GmbH

of

Frankfurt am Main/Germany

have filed a Patent Application under the title:

"Formulations for topical application of substances having an antiandrogenic action"

on 23 October 1998 at the German Patent and Trademark Office.

The attached document is a correct and accurate reproduction of the original submission for this Patent Application.

The German Patent and Trademark Office has for the time being given the Application the symbol A 61 K 31/415 of the International Patent Classification.

Munich, 23 July 1999

German Patent and Trademark Office

The President

pp

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File No: 198 48 856.4

Hoechst Marion Roussel Deutschland GmbH HMR 98/L 071 Dr.TH/Ks/sch

Description

Formulations for topical application of substances having an antiandrogenic action

Androgenic alopecia is the most frequent form of hair loss, which can occur both in men and in women. The term "androgenic alopecia" is understood as meaning hair deficiency states the cause of which is a genetically determined hypersensitivity of the hair root to 5α-dihydrotestosterone.

A typical example of androgenic alopecia is the common baldness in men. However, androgenic alopecia can also occur in women of sexually mature age - with or without the clinical features of male baldness.

A prerequisite of treatment of androgenic hair loss is early interruption of the pathogenetic processes which cause degeneration of the hair follicle. To achieve a normalization of the hair cycle, i.e. prolonging of the growth phase of the hair, it is necessary to reduce the biologically active amount of androgen at the follicle. When endocrinopathies have been ruled out and medicaments which comprise testosterone or other substances having an androgenic action have been discontinued, inhibition of androgen stimulation at the target organ is necessary. To achieve this aim, two routes are theoretically conceivable. Firstly inhibition of the activity of the 5α-reductase and therefore a reduction in the conversion of testosterone into 5α-dihydrotestosterone, for example by estrogen, and secondly blocking of the dihydrotestosterone-sensitive receptor protein, for example by antiandrogens.

Since all systemic treatment measures for androgenic alopecia are directed against the androgen action, they can be used only on women with simultaneous contraception. After introduction of oral contraceptives, it was found that the course of androgenic alopecia and its concomitant symptoms is influenced favorably or unfavorably depending on whether an estrogen-emphasized preparation or a preparation with a residual androgenic action is administered.

In the absence of another risk-free alternative with a more potent action, estrogen-containing hair lotions have hitherto been described for treatment of androgenic alopecia in men. In women, this local treatment is recommended as an assisting measure, and the main emphasis is placed on systemic treatment.

All patients are instructed to treat the region of the scalp still covered with hair and not the areas which are already bald. In many cases, it is possible to alleviate or to stop the episodes of hair loss with the aid of these local measures.

Antiandrogens having a topical action are known from French Patent 2 693 461 and US 5,411,981 (4-[3-(4-hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitriles) and from PCT Application WO 98/05654 (3-aryl-2,4-dioxo-oxazolidines), but are currently not yet generally available for treatment purposes.

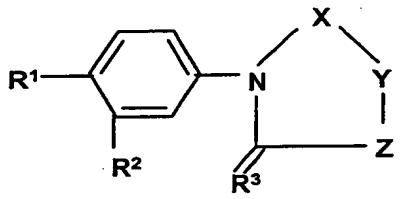
Both classes of substance show a high bonding affinity for the androgen receptor at the hair root after topical application, with virtually no systemic activity.

Because of the teratogenicity of antiandrogens, intrinsic to the substances, with an influence on sex differentiation in the late stage of pregnancy, the substances mentioned cannot be used in the form of conventional aqueous/alcoholic hair lotions because of the occurrence of precipitates of the substances at the application site after evaporation of the solvent and the associated toxicological risk of transfer of the substance to pregnant women. Furthermore, delayed release of the active compounds over a relatively long period of time, in order to avoid high systemic concentrations of the active substance and the associated occurrence of systemic antiandrogenic effects, is not guaranteed by conventional formulations for application to the scalp.

In order to make the antiandrogenic active compounds in the abovementioned patents available for a reliable and effective treatment, it was therefore necessary to discover formulations which do not have the disadvantages described for conventional scalp treatment compositions.

The object is achieved by the formulations according to the invention, comprising one or more topical antiandrogens according to US 5,411,981 or WO 98/05654, a physiologically tolerated volatile solvent or solvent mixture, a plasticizer and one or more physiologically acceptable film-forming agents which, after drying of the formulation, form flexible films which adhere to the scalp and are capable of releasing the active compounds employed in a controlled manner and over a certain period of time. Moreover, the undesirable precipitation of the active compound at the application site is prevented by the formulations according to the invention.

The invention therefore relates to a pharmaceutical formulation comprising at least one physiologically tolerated film-forming agent, at least one physiologically tolerated solvent, at least one plasticizer and a compound of the formula I



(I)

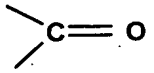
and /or a stereoisomeric form of the compound of the formula I and/or a physiologically tolerated salt of the compound of the formula I, in which

R^1 is 1) -CN,
2) $-NO_2$,
3) halogen or
4) $(C_1\text{-}C_4)$-alkyl-C(O)-OH,

R^2 is 1) $-CF_3$,
2) halogen or
3) -CN,

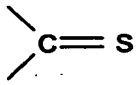
R^3 is 1) =O,
2) =S or
3) =NH,

X is 1) the radical of the part formula II



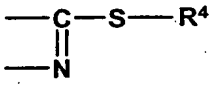
(II)

2) or the radical of the part formula III



(III)

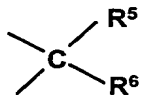
or X and Y together form the part formula IV



(IV)

in which R^4 is 1) hydrogen atom,
2) $(C_1\text{-}C_6)$-alkyl-,
3) $(C_2\text{-}C_6)$-alkenyl- or
4) $(C_1\text{-}C_6)$-alkyl-, in which alkyl is mono- to trisubstituted by
4.1 -OH,
4.2 halogen,
4.3 -O-$(C_1\text{-}C_4)$-alkyl,
4.4 -CN or
4.5 -SH,

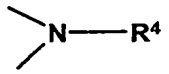
Y is 1) the radical of the part formula V



(V)

in which R^5 is a hydrogen atom or $(C_1\text{-}C_4)$-alkyl, in which alkyl is unsubstituted or mono- to tetrasubstituted by halogen, and R^6 is $(C_1\text{-}C_4)$-alkyl, in which alkyl is unsubstituted or mono- to trisubstituted, independently of one another,
a) halogen,
b) phenyl-$(CH_2)_m$-, in which phenyl is unsubstituted or mono- to trisubstituted, independently of one another by, -COOH, -CN or $-CF_3$ and m is the integer zero,1, 2, 3, 4, 5 or 6,
c) -COOH,
d) -CN or
e) $-CF_3$, or

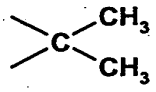
2) the radical of the part formula VI


(VI)

in which R^4 has the abovementioned meaning, and

Z is 1) -O- or

2) the radical of the part formula VII


(VII).

A preferred pharmaceutical formulation is that comprising a compound of the formula I in which

R^1 is 1) -CN,

2) $-NO_2$ or

3) halogen,

R^2 is 1) $-CF_3$ or

2) halogen,

R^3 is 1) =O or

2) =S,

X is the radical of the part formula II or III or

X and Y together form the part formula IV,

in which R^4 has the abovementioned meaning,

Y is the radical of the part formula VI,

in which R^4 has the abovementioned meaning, and

Z is the radical of the part formula VII.

A pharmaceutical formulation which is particularly preferred is that comprising a compound of the formula I in which

R^1 is -CN,

R^2 is $-CF_3$,

R^3 is =0,

X is the radical of the part formula II,

Y is the radical of the part formula VI, in which R^4 is a hydrogen atom, and

Z is -O- or the radical of the part formula VII.

Compounds of the formula I such as 4-[3-(4-hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile or 4-(5-methyl-2,4-dioxo-5-trifluoromethyl)-oxazolidin-3-yl)-2-(trifluoromethyl)benzonitrile are mentioned as especially preferred.

The term "halogen" is understood as meaning fluorine, chlorine, bromine or iodine. The term "alkyl" or "alkenyl" is understood as meaning hydrocarbon radicals in which the carbon chains are straight-chain or branched. The alkenyl radicals can furthermore also contain several double bonds. The term "physiologically tolerated solvent" is understood as meaning, for example, water or (C_1-C_6)-alcohols, such as methanol, ethanol, propanol, isopropanol, butanol, pentanol or hexanol. However, mixtures of the solvents can also be employed.

Plasticizers are substances which impart to brittle compositions, for example film-forming substances, suppleness and flexibility. The release profile of substances from films can moreover also be controlled by the nature and amount of the plasticizer added. Various classes of substances are possible suitable plasticizers, in particular ethoxylated compounds, panthenol and esters of adipic or sebacic acid.

Film-forming agents are substances of varying composition which have the feature that, when dissolved in water or other suitable solvents, they form films on the skin after the water or the solvent has evaporated, these films being capable, inter alia, of releasing incorporated active compounds in a controlled manner over a certain period of time.

In contrast to thickeners, which are added to liquid formulations to establish a certain viscosity, film-forming agents influence the viscosity of a liquid to only a small extent. A disadvantage of thickeners is the poor dispersibility of the application form.

The formulations according to the invention are primarily distinguished by a uniform release, proceeding over a certain period of time, of the compound of the formula I from the elastic film which forms after application of the formulation and adheres firmly to the skin. This ensures that therapeutically active antiandrogen concentrations are achieved at the target organ - the

hair root - over a relatively long period of time, without high blood level concentrations occurring in the short term, which of course lead to a systemic stress on the patient.

The pharmaceutical formulations are preferably liquid formulations, such as hair lotions or hair tonics, which can comprise as the main constituents water, and also aqueous (C_1-C_6)-alcohol, such as, for example, ethanol, propanol or isopropanol, and furthermore lotions and semi-solid formulations, such as emulsions, creams, gels or ointments. If appropriate, the formulations can also be in the form of aerosols.

Suitable film-forming agents are, for example, naturally occurring substances, such as alginic acid / alginates, collagen / collagen derivatives, hydrolyzed wheat proteins, carrageenan, cellulose / cellulose derivatives, chitosan / chitosan derivatives, keratin hydrolysates, protein hydrolysates, gelatin, guar gum/ guar gum derivatives, hydrolyzed elastin, hydrolyzed milk proteins, hydrolyzed silk proteins, hydrolyzed soya protein, hydrolyzed oat proteins, copolymer of hydroxyethylcellulose and dimethyldiallylammonium chloride, hyaluronic acid / hyaluronates, tragacanth and xanthan, and synthetic substances, such as acrylate / acrylamide copolymers, acrylate copolymers, acrylate / octylacrylamide copolymers, acrylic acid ester copolymers, methacrylic acid copolymers, adipic acid / dimethyl-aminohydroxypropyldiethylenetriamine copolymers, methacrylic acid / methacrylic acid ester copolymers neutralized with 2-amino-2-methylpropanol, polyacrylic acid crosslinked with pentaerythritol ethers or sugar allyl ethers, polysiloxane / polyalkyl polyether copolymers, polysiloxanes, ethylene / acrylic acid ester copolymers, ethylene / vinyl acetate copolymers, methacryloylethylbetaine / methacrylic acid copolymers, octylacrylamide / acrylic acid ester / butylaminoethylmeth-acrylic acid copolymers, quaternized polyvinylpyrrolidone-dimethylaminoethylmethacrylic acid esters, polyvinylpyrrolidone / imidazol-inium methochloride copolymers, sodium acrylate / dimethyldiallyl-ammonium chloride copolymers, dimethyldiallylammonium chloride /sodium acrylate / acrylamide terpolymer, poly(dimethylsiloxane-copolyol-phospho-panthenoate), poly(methyl vinyl ether-maleic anhydride), poly(methyl vinyl ether-maleic acid monoalkyl ester), poly(vinylpyrrolidone), terpolymers based on pyrrolidone and acrylic acid compounds, poly(vinylpyrrolidone-

dimethylaminoethylmethacrylic acid), polyvinylpyrrolidone / eicosene copolymer, polyvinylpyrrolidone / methacrylic acid ester / methacrylic acid terpolymer, polyvinylpyrrolidone / hexadecene copolymer, polyvinylpyrrolidone / polycarbamyl polyglycol ester, polyvinylpyrrolidone / vinyl acetate copolymer, vinylimidazolium methochloride / vinylpyrrolidone copolymer, acrylic acid / acrylic acid ester copolymers and terpolymer of vinylpyrrolidone, vinyl acetate and vinyl propionate.

As additives, the formulations according to the invention can also comprise circulation-promoting compounds, such as dihydralazine, diisopropylamine or diazoxide, or nifedipine, nicardipine, verapamil, miconazole, diltiazem, nisoldipine, nitrendipine, nivaldipine, isradipine, felodipine, nimodipine, gallopamil, fendiline, flunarizine, amlodipine, diperdipine, fluspirilene, primozide, fantofarone, nicergoline or cyclandelate, quinapril, lisinopril, benzazepril, captopril, ramipril, fosinopril, cifazapril trandolapril, pentoxifyllin, propentofyllin or torbafyllin, or a mixture thereof.
The formulations according to the invention can comprise as further additives the hair- and scalp-care substances customary in cosmetics and medical active compounds, such as, for example, antidandruff agents, preparations having an antiseborrheic action, substances having a keratolytic and keratoplastic action, such as salicylic acid, allantoin, sulfur preparations, urea and ceramides, antimicrobial agents, vitamins, plant or organ extracts, hormones, corticoids, hyperemic agents, such as nicotinic acid and derivatives thereof, organic acids, such as citric acid, orotic acid, liponic acid and amino acids, polyethoxylated fatty alcohols, fatty acids, sorbitan fatty acid esters, alkyl phosphates and oils, for example fatty acid esters, and furthermore preservatives, dyestuffs and perfume oils. It is essential that the additives are compatible with antiandrogenic substances and do not inhibit the hair growth action thereof.

The treatment of androgenic alopecia can be carried out reliably and effectively with the formulations according to the invention. This is an extremely important finding, in view of the poor treatment results to date.

The formulations according to the invention are also suitable for treatment of hirsutism, i.e. for avoiding undesirable hair growth, and for tretment of seborrhea and acne.

The formulations according to the invention in general comprise the active compound in an amount of 0.01 percent by weight to 10 percent by weight, preferably 0.1 to 5 percent by weight.

In liquid formulations, the amount of solvents is from 85 percent by weight to 97.5 percent by weight and the amount of plasticizer is from 0.05 percent by weight to 2.5 percent by weight. Semi-solid formulations comprise 50 percent by weight to 75 percent by weight of solvent and the amount of plasticizer is from 0.05 percent by weight to 2.5 percent by weight.

The invention furthermore relates to the use of the formulations according to the invention in cosmetics.

The formulations according to the invention are in general prepared in a manner known per se by dissolving the substances having an antiandrogenic action in the particular vehicle in question.

The formulation according to the invention has, for example, the following composition:

Example 1

4-[3-(4-Hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile	5.0%
Vinylimidazolium methochloride / vinylpyrrolidone copolymer (Luviquart® FC 550)	2.5%
Polyethoxylated hydrogenated castor oil (Cremophor® RH 410)	2.5%
Ethanol 96%	63.0%
Demineralized water	27.0%

The percentage amounts stated are based on the weight.

The formulation is prepared by dissolving the various components in water.

Example 2

4-[3-(4-Hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile	1.0%
Ethoxylated cholesterol (Solulan® C-24)	1.0%
Polyvinylpyrrolidone K 30	2.0%
Partly hydrolyzed collagen (Lanasan CL®)	1.5%
Ethyl alcohol 96%	20.0%
Preservative	
Demineralized water	74.5%

Example 3

4-[3-(4-Hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile	0.5%
Ethyl alcohol	25.0%
Methyl vinyl ether / maleic acid butyl ester copolymer (Gantrez® ES-425)	1.5%
Tris(hydroxymethyl)aminomethane	0.03%
Panthenol	0.5%
Demineralized water	72.47%

Example 4

4-[3-(4-Hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile	2.0%
Vinylimidazolium methochloride / vinylpyrrolidone copolymer (Luviquart® FC 550)	2.0%
Polyethoxylated hydrogenated castor oil (Cremophor® RH 410)	2.0%
Ethanol 96%	40.0%
Demineralized water	54.0%

Example 5

4-(5-Methyl-2,4-dioxo-5-trifluoromethyl)oxazolidin-3-yl)-2-trifluoromethylbenzonitrile	2.0%
Vinylimidazolium methochloride / vinylpyrrolidone copolymer (Luviquart® FC 550)	2.0%
Polyethoxylated hydrogenated castor oil (Cremophor® RH 410)	2.0%
Ethanol 96%	40.0%
Demineralized water	54.0%

The delayed release of the active compound from the formulations according to the invention is demonstrated in permeation tests on human skin covered with hair and without hair cover. The measurement method used enables the release of an active compound from a particular formulation and the subsequent permeation through human skin to be tested.

As a control example,

4-[3-(4-hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile	5.0%
is dissolved	
in ethanol 96%	66.5%
And demineralized water	28.5%.

Permeation test on skin covered with hair and without hair cover

The permeation of the active compound is measured by means of the time-resolved ATR technique (time-resolved infrared attenuated total reflection – see Th. M. Bayerl et al.; J. Invest. Dermatol. 105:291-295, 1995):

100 µl of the test formulation (control example) are applied to a defined area of the upper side of the human skin, covered with hair and without hair cover, lying on the measurement crystal. The permeation of the active

compound can be observed with the aid of the IR band at 1323 cm^{-1} characteristic of 4-[3-(4-hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile.

It was found here that about 90% of the amount of active compound applied permeates within 24 hours both through the skin covered with hair and through the skin without hair cover.

However, there were differences in the rate of permeation between the two pieces of skin. While the amount of active compound which has permeated already asymtotically approaches the end value after about 7 hours when skin covered with hair is used, the substance permeates virtually uniformly through skin without hair cover over 24 hours.

After application of a formulation according to the invention, for example according to Example 1, to skin containing hair follicles - such as exists with androgenic alopecia - a uniform permeation of the active compound over 24 hours, as after application of the control formulation to skin without hair cover, was likewise achieved.

Furthermore, when the formulation according to the invention was used, no precipitation of the active compound at the application site occurred after the solvent had evaporated, in contrast to the control formulation.

Patent Claims:

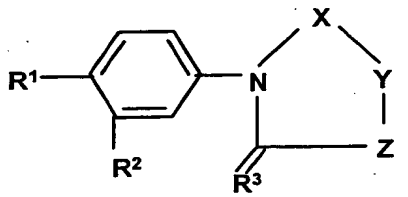
1. A formulation comprising

a) at least one physiologically tolerated film-forming agent,

b) at least one physiologically tolerated solvent,

c) at least one plasticizer and

d) a compound of the formula I



(I)

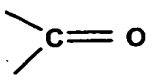
and /or a stereoisomeric form of the compound of the formula I and/or a physiologically tolerated salt of the compound of the formula I, in which

R^1 is 1) -CN,
2) $-NO_2$,
3) halogen or
4) $(C_1\text{-}C_4)$-alkyl-C(O)-OH,

R^2 is 1) $-CF_3$,
2) halogen or
3) -CN,

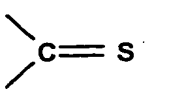
R^3 is 1) =O,
2) =S or
3) =NH,

X is 1) the radical of the part formula II



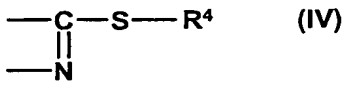
(II)

2) or the radical of the part formula III



(III)

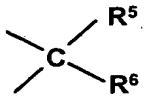
or X and Y together form the part formula IV



(IV)

in which R^4 is 1) hydrogen atom,
2) $(C_1\text{-}C_6)$-alkyl-,
3) $(C_2\text{-}C_6)$-alkenyl- or
4) $(C_1\text{-}C_6)$-alkyl-, in which alkyl is mono- to trisubstituted by
4.1 -OH,
4.2 halogen,
4.3 -O-$(C_1\text{-}C_4)$-alkyl,
4.4 -CN or
4.5 -SH,

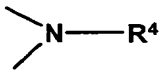
Y is 1) the radical of the part formula V



(V)

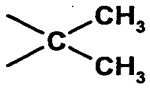
in which R^5 is a hydrogen atom or $(C_1\text{-}C_4)$-alkyl, in which alkyl is unsubstituted or mono- to tetrasubstituted by halogen, and
R^6 is $(C_1\text{-}C_4)$-alkyl, in which alkyl is unsubstituted or mono- to trisubstituted, independently of one another, by
a) halogen,
b) phenyl-$(CH_2)_m$-, in which phenyl is unsubstituted or mono- to trisubstituted, independently of one another, by -COOH, -CN or $-CF_3$ and m is the integer zero,1, 2, 3, 4, 5 or 6,
c) -COOH,
d) -CN or
e) $-CF_3$, or

2) the radical of the part formula VI,


(VI)

in which R^4 has the abovementioned meaning, and

Z is 1) -O- or
2) the radical of the part formula VII


(VII).

2. The formulation as claimed in claim 1, comprising a compound of the formula I in which

R^1 is 1) -CN,
2) $-NO_2$ or
3) halogen,

R^2 is 1) $-CF_3$ or
2) halogen,

R^3 is 1) =O or
2) =S,

X is the radical of the part formula II or III or
X and Y together form the part formula IV,
in which R^4 has the abovementioned meaning,

Y is the radical of the part formula VI,
in which R^4 has the abovementioned meaning, and

Z is the radical of the part formula VII.

3. The formulation as claimed in claim 1, comprising a compound of the formula I in which

R^1 is -CN,
R^2 is $-CF_3$,
R^3 is =0 steht,
X is the radical of the part formula II,
Y is the radical of the part formula VI and in which R^4 is a hydrogen atom, and
Z is -O- or the radical of the part formula VII.

4. The formulation as claimed in one or more of claims 1 to 3, comprising 4-[3-(4-hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile or 4-(5-methyl-2,4-dioxo-5-trifluoromethyl)-oxazolidin-3-yl)-2-(trifluoromethyl)-benzonitrile.

5. The formulation as claimed in one or more of claims 1 to 4, comprising an ethoxylated compound, panthenol or an ester of adipic acid or sebacic acid, in particular polyoxyethylated castor oil, ethoxylated cholesterol or panthenol, as the plasticizer.

6. The formulation as claimed in one or more of claims 1 to 5, comprising water or (C_1-C_6)-alcohols, such as methanol, ethanol, propanol, isopropanol, butanol, pentanol or hexanol, or mixtures of the solvents, as the solvent.

7. The formulation as claimed in one or more of claims 1 to 6, comprising naturally occurring substances, such as alginic acid / alginates, collagen / collagen derivatives, hydrolyzed wheat proteins, carrageenan, cellulose / cellulose derivatives, chitosan / chitosan derivatives, keratin hydrolysates, protein hydrolysates, gelatin, guar gum/ guar gum derivatives, hydrolyzed elastin, hydrolyzed milk proteins, hydrolyzed silk proteins, hydrolyzed soya protein, hydrolyzed oat proteins, copolymer of hydroxyethylcellulose and dimethyldiallylammonium chloride, hyaluronic acid / hyaluronates, tragacanth and xanthan, and synthetic substances, such as acrylate / acrylamide copolymers, acrylate copolymers, acrylate / octylacrylamide copolymers, acrylic acid ester copolymers, methacrylic acid copolymers, adipic acid / dimethylaminohydroxypropyldiethylenetriamine copolymers, methacrylic acid / methacrylic acid ester copolymers neutralized with 2-amino-2-methylpropanol, polyacrylic acid crosslinked with pentaerythritol ethers or sugar allyl ethers, polysiloxane / polyalkyl polyether copolymers, polysiloxanes, ethylene / acrylic acid ester copolymers, ethylene / vinyl acetate copolymers, methacryloylethyl-betaine / methacrylic acid copolymers, octylacrylamide / acrylic acid ester / butylaminoethylmethacrylic acid copolymers, quaternized polyvinylpyrrolidone-dimethylaminoethylmethacrylic acid esters,

polyvinylpyrrolidone / imidazolinium methochloride copolymers, sodium acrylate / dimethyldiallylammonium chloride copolymers, dimethyldiallylammonium chloride / sodium acrylate / acrylamide terpolymer, poly(dimethylsiloxane-copolyol-phosphopanthenoate), poly(methyl vinyl ether-maleic anhydride), poly(methyl vinyl ether-maleic acid monoalkyl ester), poly(vinylpyrrolidone), terpolymers based on pyrrolidone and acrylic acid compounds, poly(vinylpyrrolidone-dimethylaminoethylmethacrylic acid), polyvinylpyrrolidone / eicosene copolymer, polyvinylpyrrolidone / methacrylic acid ester / methacrylic acid terpolymer, polyvinylpyrrolidone / hexadecene copolymer, polyvinylpyrrolidone / polycarbamyl polyglycol ester, polyvinylpyrrolidone / vinyl acetate copolymer, vinylimidazolium methochloride / vinylpyrrolidone copolymer, acrylic acid / acrylic acid ester copolymers and terpolymer of vinylpyrrolidone, vinyl acetate and vinyl propionate, as the film-forming agent.

8. The formulation as claimed in one or more of claims 1 to 7, which comprises as a further additive at least one circulation-promoting compound, such as dihydralazine, diisopropylamine or diazoxide, or nifedipine, nicardipine, verapamil, miconazole, diltiazem, nisoldipine, nitrendipine, nivaldipine, isradipine, felodipine, nimodipine, gallopamil, fendiline, flunarizine or amlodipine, diperdipine, fluspirilene, primozide, fantofarone, nicergoline, cyclandelate, or quinapril, lisinopril, benzazepril, captopril, ramipril, fosinopril, cifazapril, trandolapril, pentoxifyllin, propentofyllin or torbafyllin, or a mixture thereof.

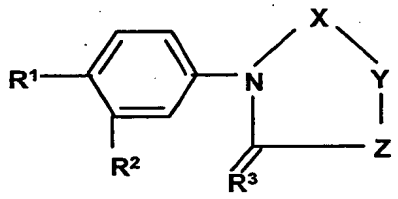
9. The use of a formulation as claimed in one or more of claims 1 to 8 for the preparation of a medicament for treatment of androgenic alopecia or hirsutism, i.e. for avoiding undesirable hair growth, and for treatment of seborrhea and acne.

10. The use of a formulation as claimed in one or more of claims 1 to 8 in cosmetics.

Abstract:

Formulations for topical application of substances having an antiandrogenic action

A formulation comprising at least one physiologically tolerated film-forming agent, at least one physiologically tolerated solvent, at least one plasticizer and a compound of the formula I



(I)

is suitable for treatment of androgenic alopecia or hirsutism, i.e. for avoiding undesirable hair growth, and for treatment of seborrhea and acne, and can furthermore be employed in cosmetics.

UNITED STATES PATENT AND TRADEMARK OFFICE

I, Charles Edward SITCH BA,

Managing Director of RWS Group Ltd UK Translation Division, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare;

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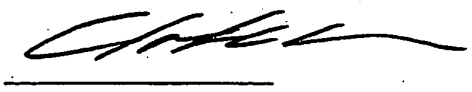
2. That the translator responsible for the attached translation is well acquainted with the German and English languages.

3. That the attached is, to the best of RWS Group Ltd knowledge and belief, a true translation into the English language of the accompanying copy of the specification filed with the application for a patent in Germany on 12 January 1999 under the number 199 00 749.7 and the official certificate attached thereto.

4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application in the United States of America or any patent issuing thereon.



For and on behalf of RWS Group Ltd

The 19th day of February 2008

FEDERAL REPUBLIC OF GERMANY

Certificate

Hoechst Marion Roussel Deutschland GmbH

of

Frankfurt am Main/Germany

have filed a Patent Application under the title:

"Formulations for topical application of substances having an antiandrogenic action"

on 12 January 1999 at the German Patent and Trademark Office.

The attached document is a correct and accurate reproduction of the original submission for this Patent Application.

The German Patent and Trademark Office has for the time being given the Application the symbol A 61 K 7/06 of the International Patent Classification.

Munich, 26 July 1999

German Patent and Trademark Office

The President

pp

Seiler

File No: 199 00 749.7

Hoechst Marion Roussel Deutschland GmbH HMR 98/L 002Dr.TH/Ks/sch

Description

Formulations for topical application of substances having an antiandrogenic action

Androgenic alopecia is the most frequent form of hair loss, which can occur both in men and in women. The term "androgenic alopecia" is understood as meaning hair deficiency states the cause of which is a genetically determined hypersensitivity of the hair root to 5α-dihydrotestosterone.

A typical example of androgenic alopecia is the common baldness in men. However, androgenic alopecia can also occur in women of sexually mature age - with or without the clinical features of male baldness.

A prerequisite of treatment of androgenic hair loss is early interruption of the pathogenetic processes which cause degeneration of the hair follicle. To achieve a normalization of the hair cycle, i.e. prolonging of the growth phase of the hair, it is necessary to reduce the biologically active amount of androgen at the follicle. When endocrinopathies have been ruled out and medicaments which comprise testosterone or other substances having an androgenic action have been discontinued, inhibition of androgen stimulation at the target organ is necessary. To achieve this aim, two routes are theoretically conceivable. Firstly inhibition of the activity of the 5α-reductase and therefore a reduction in the conversion of testosterone into 5α-dihydrotestosterone, for example by estrogen, and secondly blocking of the dihydrotestosterone-sensitive receptor protein, for example by antiandrogens.

Since all systemic treatment measures for androgenic alopecia are directed against the androgen action, they can be used on women of child-bearing age only with simultaneous contraception. After introduction of oral contraceptives, it was found that the course of androgenic alopecia and its concomitant symptoms is influenced favorably or unfavorably depending on whether an estrogen-emphasized preparation or a preparation with a residual androgenic action is administered.

In the absence of another risk-free alternative with a more potent action, estrogen-containing hair lotions have hitherto been described for treatment of androgenic alopecia in men. In women, this local treatment is recommended as an assisting measure, and the main emphasis is placed on systemic treatment.

All patients are instructed to treat the region of the scalp still covered with hair and not the areas which are already bald. In many cases, it is possible to alleviate or to stop the episodes of hair loss with the aid of these local measures.

Antiandrogens having a topical action are known from French Patent 2 693 461 and US 5,411,981 (4-[3-(4-hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitriles) and from PCT Application WO 98/05654 (3-aryl-2,4-dioxo-oxazolidines), but are currently not yet generally available for treatment purposes.

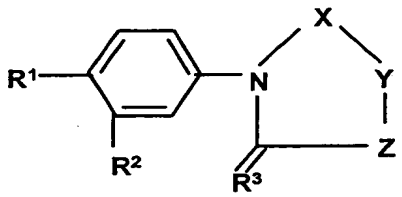
Both classes of substance show a high bonding affinity for the androgen receptor at the hair root after topical application, with virtually no systemic activity.

Because of the teratogenicity of antiandrogens, intrinsic to the substances, with an influence on sex differentiation in the late stage of pregnancy, the substances mentioned cannot be used in the form of conventional aqueous/alcoholic hair lotions because of the occurrence of precipitates of the substances at the application site after evaporation of the solvent and the associated toxicological risk of transfer of the substance to pregnant women. Furthermore, delayed release of the active compounds over a relatively long period of time, in order to avoid high systemic concentrations of the active substance and the associated occurrence of systemic antiandrogenic effects, is not guaranteed by conventional formulations for application to the scalp.

In order to make the antiandrogenic active compounds in the abovementioned patents available for a reliable and effective treatment, it was therefore necessary to discover formulations which do not have the disadvantages described for conventional scalp treatment compositions.

The object is achieved by the formulations according to the invention, comprising one or more topical antiandrogens according to US 5,411,981 or WO 98/05654, a physiologically tolerated volatile solvent or solvent mixture, a plasticizer and one or more physiologically acceptable film-forming agents which, after drying of the formulation, form flexible films which adhere to the scalp and are capable of releasing the active compounds employed in a controlled manner and over a certain period of time. Moreover, the undesirable precipitation of the active compound at the application site is prevented by the formulations according to the invention.

The invention therefore relates to a pharmaceutical formulation comprising at least one physiologically tolerated film-forming agent, at least one physiologically tolerated solvent, at least one plasticizer and a compound of the formula I



(I)

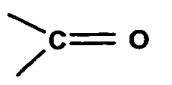
and /or a stereoisomeric form of the compound of the formula I and/or a physiologically tolerated salt of the compound of the formula I, in which

R^1 is 1) -CN,
2) $-NO_2$,
3) halogen or
4) $(C_1\text{-}C_4)$-alkyl-C(O)-OH,

R^2 is 1) $-CF_3$,
2) halogen or
3) -CN,

R^3 is 1) =O,
2) =S or
3) =NH,

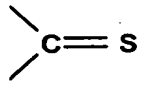
X is 1) the radical of the part formula II



(II)

or

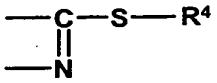
2) the radical of the part formula III



(III)

or

X and Y together form the part formula IV



(IV)

in which R^4 is 1) hydrogen atom,

2) $(C_1\text{-}C_6)$-alkyl-,

3) $(C_2\text{-}C_6)$-alkenyl- or

4) $(C_1\text{-}C_6)$-alkyl-, in which alkyl is mono- to trisubstituted by

4.1 -OH,

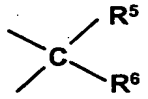
4.2 halogen,

4.3 -O-$(C_1\text{-}C_4)$-alkyl,

4.4 -CN or

4.5 -SH,

Y is 1) the radical of the part formula V



(V)

in which R^5 is a hydrogen atom or $(C_1\text{-}C_4)$-alkyl, in which alkyl is unsubstituted or mono- to tetrasubstituted by halogen, and R^6 is $(C_1\text{-}C_4)$-alkyl, in which alkyl is unsubstituted or mono- to trisubstituted, independently of one another,

a) halogen,

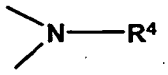
b) phenyl-$(CH_2)_m$-, in which phenyl is unsubstituted or mono- to trisubstituted, independently of one another by, -COOH, -CN or $-CF_3$ and m is the integer zero,1, 2, 3, 4, 5 or 6,

c) -COOH,

d) -CN or

e) $-CF_3$, or

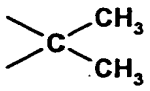
2) the radical of the part formula VI


(VI)

in which R^4 has the abovementioned meaning, and

Z is 1) -O- or

2) the radical of the part formula VII


(VII).

A preferred pharmaceutical formulation is that comprising a compound of the formula I in which

R^1 is 1) -CN,

2) $-NO_2$ or

3) halogen,

R^2 is 1) $-CF_3$ or

2) halogen,

R^3 is 1) =O or

2) =S,

X is the radical of the part formula II or III or

X and Y together form the part formula IV,

in which R^4 has the abovementioned meaning,

Y is the radical of the part formula VI,

in which R^4 has the abovementioned meaning, and

Z is the radical of the part formula VII.

A pharmaceutical formulation which is particularly preferred is that comprising a compound of the formula I in which

R^1 is -CN,

R^2 is $-CF_3$,

R^3 is =0,

X is the radical of the part formula II,

Y is the radical of the part formula VI, in which R^4 is a hydrogen atom, and

Z is -O- or the radical of the part formula VII.

Compounds of the formula I such as 4-[3-(4-hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile or 4-(5-methyl-2,4-dioxo-5-trifluoromethyl)-oxazolidin-3-yl)-2-(trifluoromethyl)benzonitrile are mentioned as especially preferred.

The term "halogen" is understood as meaning fluorine, chlorine, bromine or iodine. The term "alkyl" or "alkenyl" is understood as meaning hydrocarbon radicals in which the carbon chains are straight-chain or branched. The alkenyl radicals can furthermore also contain several double bonds. The term "physiologically tolerated solvent" is understood as meaning, for example, water or (C_1-C_6)-alcohols, such as methanol, ethanol, propanol, isopropanol, butanol, pentanol or hexanol. However, mixtures of the solvents can also be employed.

Plasticizers are substances which impart to brittle compositions, for example film-forming substances, suppleness and flexibility. The release profile of substances from films can moreover also be controlled by the nature and amount of the plasticizer added. Various classes of substances are possible suitable plasticizers, in particular ethoxylated compounds, panthenol and esters of adipic or sebacic acid.

Film-forming agents are substances of varying composition which have the feature that, when dissolved in water or other suitable solvents, they form films on the skin after the water or the solvent has evaporated, these films being capable, inter alia, of releasing incorporated active compounds in a controlled manner over a certain period of time.

In contrast to thickeners, which are added to liquid formulations to establish a certain viscosity, film-forming agents influence the viscosity of a liquid to only a small extent. A disadvantage of thickeners is the poor dispersibility of the application form.

The formulations according to the invention are primarily distinguished by a uniform release, proceeding over a certain period of time, of the compound of the formula I from the elastic film which forms after application of the formulation and adheres firmly to the skin. This ensures that therapeutically active antiandrogen concentrations are achieved at the target organ - the hair root - over a relatively long period of time, without high blood level

concentrations occurring in the short term, which of course lead to a systemic stress on the patient.

The pharmaceutical formulations are preferably liquid formulations, such as hair lotions or hair tonics, which can comprise as the main constituents water, and also aqueous (C_1-C_6)-alcohol, such as, for example, ethanol, propanol or isopropanol, and furthermore lotions and semi-solid formulations, such as emulsions, creams, gels or ointments. If appropriate, the formulations can also be in the form of aerosols.

Suitable film-forming agents are, for example, naturally occurring substances, such as alginic acid / alginates, collagen / collagen derivatives, hydrolyzed wheat proteins, carrageenan, cellulose / cellulose derivatives, chitosan / chitosan derivatives, keratin hydrolysates, protein hydrolysates, gelatin, guar gum/ guar gum derivatives, hydrolyzed elastin, hydrolyzed milk proteins, hydrolyzed silk proteins, hydrolyzed soya protein, hydrolyzed oat proteins, copolymer of hydroxyethylcellulose and dimethyldiallylammonium chloride, hyaluronic acid / hyaluronates, tragacanth and xanthan, and synthetic substances, such as acrylate / acrylamide copolymers, acrylate copolymers, acrylate / octylacrylamide copolymers, acrylic acid ester copolymers, methacrylic acid copolymers, adipic acid / dimethyl-aminohydroxypropyldiethylenetriamine copolymers, methacrylic acid / methacrylic acid ester copolymers neutralized with 2-amino-2-methylpropanol, polyacrylic acid crosslinked with pentaerythritol ethers or sugar allyl ethers, polysiloxane / polyalkyl polyether copolymers, polysiloxanes, ethylene / acrylic acid ester copolymers, ethylene / vinyl acetate copolymers, methacryloylethylbetaine / methacrylic acid copolymers, octylacrylamide / acrylic acid ester / butylaminoethylmeth-acrylic acid copolymers, quaternized polyvinylpyrrolidone-dimethylaminoethylmethacrylic acid esters, polyvinylpyrrolidone / imidazol-inium methochloride copolymers, sodium acrylate / dimethyldiallyl-ammonium chloride copolymers, dimethyldiallylammonium chloride /sodium acrylate / acrylamide terpolymer, poly(dimethylsiloxane-copolyol-phospho-panthenoate), poly(methyl vinyl ether-maleic anhydride), poly(methyl vinyl ether-maleic acid monoalkyl ester), poly(vinylpyrrolidone), terpolymers based on pyrrolidone and acrylic acid compounds, poly(vinylpyrrolidone-dimethylaminoethylmethacrylic acid), polyvinylpyrrolidone / eicosene copolymer, polyvinylpyrrolidone / methacrylic acid ester / methacrylic acid

terpolymer, polyvinylpyrrolidone / hexadecene copolymer, polyvinylpyrrolidone / polycarbamyl polyglycol ester, polyvinylpyrrolidone / vinyl acetate copolymer, vinylimidazolium methochloride / vinylpyrrolidone copolymer, acrylic acid / acrylic acid ester copolymers and terpolymer of vinylpyrrolidone, vinyl acetate and vinyl propionate.

As additives, the formulations according to the invention can also comprise at least one circulation-promoting compound, such as dihydralazine, diisopropylamine or diazoxide, or calcium antagonists, such as nifedipine, nicardipine, verapamil, diltiazem, nisoldipine, nitrendipine, nivaldipine, isradipine, felodipine, nimodipine, gallopamil, fendiline, flunarizine, amlodipine, diperdipine, fluspirilene, primozide, fantofarone, nicergoline or cyclandelate, 6-amino-4-piperidino-1,2-dihydro-1-hydroxy-2-iminopyrimidine (minoxidil), angiotensin converting enzyme inhibitors, such as quinapril, lisinopril, benzazepril, captopril, ramipril, fosinopril, cifazapril or trandolapril, methylxanthine compounds, such as pentoxifyllin, propentofyllin or torbafyllin, or a mixture thereof.
Suitable additives are also at least one sodium channel opener, such as 1-cyano-2-(1,1-dimethyl-propyl)-3-(3-pyridyl)guanidine, or 5-alpha-reductase inhibitors, such as N-tert-butyl-3-oxo-4aza-5α-androst-1-ene-17β-carboxamide. Other suitable additives are also at least one hair growth-promoting compound, such as an inner salt of 2,4-diamino-6-alkoxy-3-sulfoxypyrimidine hydroxide having 1 to 6 carbon atoms in the alkoxy radical, as described in EP 0 427 625; for example, the inner salt of 2,4-diamino-6-butoxy-3-sulfoxypyrimidine hydroxide, or pyridine 1-oxide derivatives as described in WO 92 21317, for example 2,6-diamino-4-piperidinopyridine, or 2,6-diamino-1,3,5-triazine derivatives as described in WO 91 19701, for example 2,6-diamino-4-butoxy-1,3,5-triazine 1-oxide. Mixtures of the additives mentioned are also suitable.
The formulations according to the invention can comprise as further additives the hair- and scalp-care substances customary in cosmetics and medical active compounds, such as, for example, antidandruff agents, preparations having an antiseborrheic action, substances having a keratolytic and keratoplastic action, such as salicylic acid, allantoin, sulfur preparations, urea and ceramides, antimicrobial agents, vitamins, plant or organ extracts, hormones, corticoids, hyperemic agents, such as nicotinic acid and derivatives thereof, organic acids, such as citric acid, orotic acid, liponic acid and amino acids, polyethoxylated fatty alcohols, fatty acids, sorbitan fatty acid esters, alkyl phosphates and oils, for example fatty acid

esters, and furthermore preservatives, dyestuffs and perfume oils. It is essential that the additives are compatible with antiandrogenic substances and do not inhibit the hair growth action thereof.

The treatment of androgenic alopecia can be carried out reliably and effectively with the formulations according to the invention. This is an extremely important finding, in view of the poor treatment results to date.

The formulations according to the invention are also suitable for treatment of hirsutism, i.e. for avoiding undesirable hair growth, and for tretment of seborrhea and acne.

The formulations according to the invention in general comprise the active compound in an amount of 0.01 percent by weight to 10 percent by weight, preferably 0.1 to 5 percent by weight.

In liquid formulations, the amount of solvents is from 85 percent by weight to 97.5 percent by weight and the amount of plasticizer is from 0.05 percent by weight to 2.5 percent by weight. Semi-solid formulations comprise 50 percent by weight to 75 percent by weight of solvent and the amount of plasticizer is from 0.05 percent by weight to 2.5 percent by weight.

The invention furthermore relates to the use of the formulations according to the invention in cosmetics.

The formulations according to the invention are in general prepared in a manner known per se by dissolving the substances having an antiandrogenic action in the particular vehicle in question.

The formulation according to the invention has, for example, the following composition:

Example 1

4-[3-(4-Hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile	5.0%
Vinylimidazolium methochloride / vinylpyrrolidone copolymer (Luviquart® FC 550)	2.5%

Polyethoxylated hydrogenated castor oil (Cremophor® RH 410)	2.5%
Ethanol 96%	63.0%
Demineralized water	27.0%

The percentage amounts stated are based on the weight.

The formulation is prepared by dissolving the various components in water.

Example 2

4-[3-(4-Hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile	1.0%
Ethoxylated cholesterol (Solulan® C-24)	1.0%
Polyvinylpyrrolidone K 30	2.0%
Partly hydrolyzed collagen (Lanasan CL®)	1.5%
Ethyl alcohol 96%	20.0%
Preservative	
Demineralized water	74.5%

Example 3

4-[3-(4-Hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile	0.5%
Ethyl alcohol	25.0%
Methyl vinyl ether / maleic acid butyl ester copolymer (Gantrez® ES-425)	1.5%
Tris(hydroxymethyl)aminomethane	0.03%
Panthenol	0.5%
Demineralized water	72.47%

Example 4

4-[3-(4-Hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile	2.0%

Vinylimidazolium methochloride / vinylpyrrolidone copolymer (Luviquart® FC 550)	2.0%
Polyethoxylated hydrogenated castor oil (Cremophor® RH 410)	2.0%
Ethanol 96%	40.0%
Demineralized water	54.0%

Example 5

4-(5-Methyl-2,4-dioxo-5-trifluoromethyl)oxazolidin-3-yl)-2-trifluoromethylbenzonitrile	2.0%
Vinylimidazolium methochloride / vinylpyrrolidone copolymer (Luviquart® FC 550)	2.0%
Polyethoxylated hydrogenated castor oil (Cremophor® RH 410)	2.0%
Ethanol 96%	40.0%
Demineralized water	54.0%

The delayed release of the active compound from the formulations according to the invention is demonstrated in permeation tests on human skin covered with hair and without hair cover. The measurement method used enables the release of an active compound from a particular formulation and the subsequent permeation through human skin to be tested.

As a control example,

4-[3-(4-hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile	5.0%
is dissolved	
in ethanol 96%	66.5%
and demineralized water	28.5%.

Permeation test on skin covered with hair and without hair cover

The permeation of the active compound is measured by means of the time-resolved ATR technique (time-resolved infrared attenuated total reflection – see Th. M. Bayerl et al.; J. Invest. Dermatol. 105:291-295, 1995):

100 µl of the test formulation (control example) are applied to a defined area of the upper side of the human skin, covered with hair and without hair cover, lying on the measurement crystal. The permeation of the active compound can be observed with the aid of the IR band at 1323 cm^{-1} characteristic of 4-[3-(4-hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-imidazolidinyl]-2-(trifluoromethyl)benzonitrile.

It was found here that about 90% of the amount of active compound applied permeates within 24 hours both through the skin covered with hair and through the skin without hair cover.

However, there were differences in the rate of permeation between the two pieces of skin. While the amount of active compound which has permeated already asymtotically approaches the end value after about 7 hours when skin covered with hair is used, the substance permeates virtually uniformly through skin without hair cover over 24 hours.

After application of a formulation according to the invention, for example according to Example 1, to skin containing hair follicles - such as exists with androgenic alopecia - a uniform permeation of the active compound over 24 hours, as after application of the control formulation to skin without hair cover, was likewise achieved.

Furthermore, when the formulation according to the invention was used, no precipitation of the active compound at the application site occurred after the solvent had evaporated, in contrast to the control formulation.

Patent Claims:

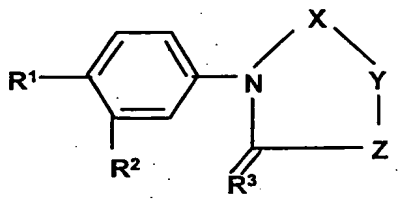
1. A formulation comprising

a) at least one physiologically tolerated film-forming agent,

b) at least one physiologically tolerated solvent,

c) at least one plasticizer and

d) a compound of the formula I



(I)

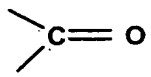
and /or a stereoisomeric form of the compound of the formula I and/or a physiologically tolerated salt of the compound of the formula I, in which

R^1 is 1) -CN,
2) $-NO_2$,
3) halogen or
4) $(C_1\text{-}C_4)$-alkyl-C(O)-OH,

R^2 is 1) $-CF_3$,
2) halogen or
3) -CN,

R^3 is 1) =O,
2) =S or
3) =NH,

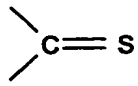
X is 1) the radical of the part formula II



(II)

or

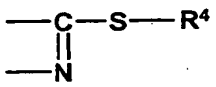
2) the radical of the part formula III



(III)

or

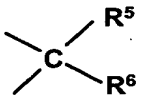
X and Y together form the part formula IV



(IV)

in which R^4 is 1) hydrogen atom,
2) $(C_1\text{-}C_6)$-alkyl-,
3) $(C_2\text{-}C_6)$-alkenyl- or
4) $(C_1\text{-}C_6)$-alkyl-, in which alkyl is mono- to trisubstituted by
4.1 -OH,
4.2 halogen,
4.3 -O-$(C_1\text{-}C_4)$-alkyl,
4.4 -CN or
4.5 -SH,

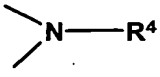
Y is 1) the radical of the part formula V



(V)

in which R^5 is a hydrogen atom or $(C_1\text{-}C_4)$-alkyl, in which alkyl is unsubstituted or mono- to tetrasubstituted by halogen, and
R^6 is $(C_1\text{-}C_4)$-alkyl, in which alkyl is unsubstituted or mono- to trisubstituted, independently of one another, by
a) halogen,
b) phenyl-$(CH_2)_m$-, in which phenyl is unsubstituted or mono- to trisubstituted, independently of one another, by -COOH, -CN or $-CF_3$ and m is the integer zero,1, 2, 3, 4, 5 or 6,
c) -COOH,
d) -CN or
e) $-CF_3$, or

2) the radical of the part formula VI,

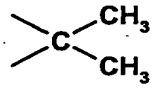


(VI)

in which R^4 has the abovementioned meaning, and

Z is 1) -O- or

2) the radical of the part formula VII



(VII).

2. The formulation as claimed in claim 1, comprising a compound of the formula I in which

R^1 is 1) -CN,

2) $-NO_2$ or

3) halogen,

R^2 is 1) $-CF_3$ or

2) halogen,

R^3 is 1) =O or

2) =S,

X is the radical of the part formula II or III or

X and Y together form the part formula IV,
in which R^4 has the abovementioned meaning,

Y is the radical of the part formula VI,
in which R^4 has the abovementioned meaning, and

Z is the radical of the part formula VII.

3. The formulation as claimed in claim 1, comprising a compound of the formula I in which

R^1 is -CN,

R^2 is $-CF_3$,

R^3 is =0 steht,

X is the radical of the part formula II,

Y is the radical of the part formula VI and in which R^4 is a hydrogen atom, and

Z is -O- or the radical of the part formula VII.

4. The formulation as claimed in one or more of claims 1 to 3, comprising 4-[3-(4-hydroxybutyl)-4,4-dimethyl-2,5-dioxo-1-

imidazolidinyl]-2-(trifluoromethyl)benzonitrile or 4-(5-methyl-2,4-dioxo-5-trifluoromethyl)-oxazolidin-3-yl)-2-(trifluoromethyl)-benzonitrile.

5. The formulation as claimed in one or more of claims 1 to 4, comprising an ethoxylated compound, panthenol or an ester of adipic acid or sebacic acid, in particular polyoxyethylated castor oil, ethoxylated cholesterol or panthenol, as the plasticizer.

6. The formulation as claimed in one or more of claims 1 to 5, comprising water or (C_1-C_6)-alcohols, such as methanol, ethanol, propanol, isopropanol, butanol, pentanol or hexanol, or mixtures of the solvents, as the solvent.

7. The formulation as claimed in one or more of claims 1 to 6, comprising naturally occurring substances, such as alginic acid / alginates, collagen / collagen derivatives, hydrolyzed wheat proteins, carrageenan, cellulose / cellulose derivatives, chitosan / chitosan derivatives, keratin hydrolysates, protein hydrolysates, gelatin, guar gum/ guar gum derivatives, hydrolyzed elastin, hydrolyzed milk proteins, hydrolyzed silk proteins, hydrolyzed soya protein, hydrolyzed oat proteins, copolymer of hydroxyethylcellulose and dimethyldiallylammonium chloride, hyaluronic acid / hyaluronates, tragacanth and xanthan, and synthetic substances, such as acrylate / acrylamide copolymers, acrylate copolymers, acrylate / octylacrylamide copolymers, acrylic acid ester copolymers, methacrylic acid copolymers, adipic acid / dimethylaminohydroxypropyldiethylenetriamine copolymers, methacrylic acid / methacrylic acid ester copolymers neutralized with 2-amino-2-methylpropanol, polyacrylic acid crosslinked with pentaerythritol ethers or sugar allyl ethers, polysiloxane / polyalkyl polyether copolymers, polysiloxanes, ethylene / acrylic acid ester copolymers, ethylene / vinyl acetate copolymers, methacryloylethyl-betaine / methacrylic acid copolymers, octylacrylamide / acrylic acid ester / butylaminoethylmethacrylic acid copolymers, quaternized polyvinylpyrrolidone-dimethylaminoethylmethacrylic acid esters, polyvinylpyrrolidone / imidazolinium methochloride copolymers, sodium acrylate / dimethyldiallylammonium chloride copolymers, dimethyldiallylammonium chloride / sodium acrylate / acrylamide

terpolymer, poly(dimethylsiloxane-copolyol-phosphopanthenoate), poly(methyl vinyl ether-maleic anhydride), poly(methyl vinyl ether-maleic acid monoalkyl ester), poly(vinylpyrrolidone), terpolymers based on pyrrolidone and acrylic acid compounds, poly(vinylpyrrolidone-dimethylaminoethylmethacrylic acid), polyvinylpyrrolidone / eicosene copolymer, polyvinylpyrrolidone / methacrylic acid ester / methacrylic acid terpolymer, polyvinylpyrrolidone / hexadecene copolymer, polyvinylpyrrolidone / polycarbamyl polyglycol ester, polyvinylpyrrolidone / vinyl acetate copolymer, vinylimidazolium methochloride / vinylpyrrolidone copolymer, acrylic acid / acrylic acid ester copolymers and terpolymer of vinylpyrrolidone, vinyl acetate and vinyl propionate, as the film-forming agent.

8. The formulation as claimed in one or more of claims 1 to 7, which comprises as a further additive at least one circulation-promoting compound, such as dihydralazine, diisopropylamine or diazoxide, or calcium antagonists, such as nifedipine, nicardipine, verapamil, diltiazem, nisoldipine, nitrendipine, nivaldipine, isradipine, felodipine, nimodipine, gallopamil, fendiline, flunarizine, amlodipine, diperdipine, fluspirilene, primozide, fantofarone, nicergoline or cyclandelate, 6-amino-4-piperidino-1,2-dihydro-1-hydroxy-2-iminopyrimidine (minoxidil), angiotensin converting enzyme inhibitors, such as quinapril, lisinopril, benzazepril, captopril, ramipril, fosinopril, cifazapril or trandolapril, methylxanthine compounds, such as pentoxifyllin, propentofyllin or torbafyllin, or a mixture thereof, or comprises at least one sodium channel opener, such as 1-cyano-2-(1,1-dimethyl-propyl)-3-(3-pyridyl)guanidine, or 5-alpha-reductase inhibitors, such as N-tert-butyl-3-oxo-4aza-5α-androst-1-ene-17β-carboxamide, or at least one hair growth-promoting compound, such as inner salts of 2,4-diamino-6-alkoxy-3-sulfoxypyrimidine hydroxide having 1 to 6 carbon atoms in the alkoxy radical, such as the inner salt of 2,4-diamino-6-butoxy-3-sulfoxypyrimidine hydroxide, or pyridine 1-oxide derivatives, such as 2,6-diamino-4-piperidinopyridine, or 2,6-diamino-1,3,5-triazine derivatives, such as 2,6-diamino-4-butoxy-1,3,5-triazine 1-oxide or mixtures thereof.

9. The use of a formulation as claimed in one or more of claims 1 to 8 for the preparation of a medicament for treatment of androgenic

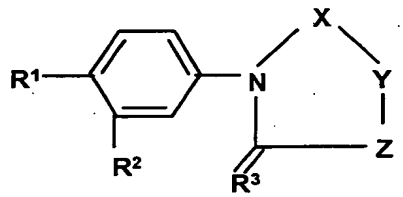
alopecia or hirsutism, i.e. for avoiding undesirable hair growth, and for treatment of seborrhea and acne.

10. The use of a formulation as claimed in one or more of claims 1 to 8 in cosmetics.

Abstract:

Formulations for topical application of substances having an antiandrogenic action

A formulation comprising at least one physiologically tolerated film-forming agent, at least one physiologically tolerated solvent, at least one plasticizer and a compound of the formula I



(I)

is suitable for treatment of androgenic alopecia or hirsutism, i.e. for avoiding undesirable hair growth, and for treatment of seborrhea and acne, and can furthermore be employed in cosmetics.